REMARKS

I. Status of the Claims

Claims 13-14, 16, 32-33, and 36-37 had been previously canceled, and claims 18, and 40-43 have been canceled in this response, all without prejudice or disclaimer. Claims 1-8, 10-12, 19-31, 34, and 35 were previously withdrawn. In this response, claims 9 and 38 have been amended. With entry of this amendment, claims 9, 15, 17, 38 and 39 are under examination in the application.

Claim 9 has been amended to recite "cultivating a cell that has an insulin gene or a gene under the control of an insulin promoter and that produces a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 or a partial peptide thereof in the presence and absence of a test substance." Exemplary support for the amendments may be found in the specification and claims as filed, for instance at least at page 32, line 24 to page 33, line 3, and at page 33, lines 17-34, of the as-filed specification. Claim 38 has been amended to more precisely recite the feature being amended. Accordingly, there is no written description issue raised by this amendment.

Applicants note with appreciation that all previous rejections have been withdrawn.

II. Information Disclosure Statement

Applicants would like to bring to the Examiner's attention the List of References Cited by Applicant and Considered by Examiner, which the Examiner initialed and attached to the Office Action mailed August 12, 2009. In the PTO/SB/08 form, the Examiner crossed out the Communication Pursuant to Article 94(3) EPC ("Communication") for European Patent Application No. 03 772 678.3 (European

counterpart of the instant application), stating that the format is improper and there is no author or public availability date. Applicants note that the European Patent Application No. 03 772 678.3 was published on August 18, 2005. Therefore, the public availability date of the Communication is the mailing date, November 18, 2008, as indicated in the PTO/SB/08 form. Applicants further note that the author of the Communication is the Examiner at the European Patent Office. Therefore, Applicants enclose a new PTO/SB/08 form citing the Communication, and respectfully request that the Examiner consider and initial the reference.

III. Objection to Claims

Citing to MPEP 608.01(m), the Office has objected to claims 9, 15, 17, 18, and 38-43, on the ground that "the instant claims consist only of sentence fragments." Office Action at page 2. Applicants respectfully note that at page 80 of the originally filed application, the claims are introduced with the phrase "What is claimed is." This comports with MPEP 608.01(m). The Office further states that each method step must be indented (*Id*), and Applicants have indented the different steps of claim 9. Claims 18 and 40-43 have been canceled. Claims 15, 17, and 38-39 depend from claim 9. Applicants respectfully request withdrawal of the objection in view of the amendments.

IV. Rejections Under 35 U.S.C. § 103(a)

The Office has rejected claims 9, 15, 17, 18, and 38-43 under 35 U.S.C. § 103(a) for allegedly being unpatentable over U.S. Patent No. 6,617,440 ("the '440 patent"), in view of Ihara et al. (2001, *Diabetologia*, 44(sup1):A120) ("Ihara") and Flyvbjerg et al. (2002, *Diabetes* 51: 3090-3094) ("Flyvbjerg"). *See* Office Action at pages 2-4. Specifically, the Office contends that:

> "The '440 patent teaches a screening method for a therapeutic substance (a compound which exhibits the ability to promote muscle growth) . . . comprising cultivating a cell . . . and comparing the expression of a gene in the presence or absence of a test compound. Said method further includes the assaying of mRNA expression."

Office Action at page 3. The Office acknowledges that the '440 patent "differs from the claimed invention in that it does not teach comparing the expression of a gene encoding the protein of SEQ ID NO:2." *Id.* However, the Office maintains that:

> Ihara et al. teaches the protein of SEQ ID NO:2 (TSC-22), is associated with diabetes. In particular, the expression of the gene of SEQ ID NO:1 can be used as a marker for insulin expression. TSC-22 inhibits insulin expression such that a measure of TSC-22 expression can be used as a measure of insulin expression and the reduction of TSC-22 expression is an indication of increased insulin expression.

Id. The Office further contends that Flyvbjerg et al. teaches that diabetic nephropathy in type 2 diabetic patients is a frequent complication and that it is the most common cause of end stage renal failure in the Western World. *Id.*

The Office thus concludes that:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the screening method of the '440 patent employing the measuring of the expression of the TSC-22 gene of Ihara et al. given the relationship of TSC-22 expression and insulin expression. Said method could be used as a method for screening test substances for their effect on TSC-22 expression as a measure of their efficacy as a therapeutic for the treatment of diabetes.

Office Action at page 3.

Applicants respectfully traverse. As amended, independent claim 9 provides a screening method that is neither taught nor suggested by any of the cited references,

either alone or in combination. With indentations to better reflect the different aspects of the claimed method, amended claim 9 recites:

> A screening method for a prophylactic or therapeutic substance for a renal disease, comprising
>
> (a) cultivating a cell
>
> that has an insulin gene or a gene under the control of an insulin promoter and
>
> that produces a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 or a partial peptide thereof
>
> in the presence and absence of a test substance,
>
> (b) comparing the expression level of the insulin gene or the gene under the control of the insulin promoter in the presence and absence of the test substance, and
>
> (c) selecting the test substance that changes the expression level of the insulin gene or the gene under the control of the insulin promoter as a candidate for the prophylactic or therapeutic substance.

Thus, as set forth in step (a) of the claimed screening method, the cell (1) has an insulin gene, or a gene under the control of an insulin promoter, and also (2) produces a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 or a partial peptide thereof ("TSC-22"). This cell is cultivated in the presence or absence of a test substance that targets TSC-22. As set forth in step (b), the expression level of the insulin gene, or a gene under the control of an insulin promoter, is compared to determine the effect of the test substance on TSC-22, which means that the insulin gene, or a gene under the control of an insulin promoter, is used as a reporter or indicator for changes in the expression and/or activity of TSC-22. And as set forth in step (c), the test substance that changes the expression

level of the insulin gene, or a gene under the control of an insulin promoter, is selected. With these components, such a method screens for a test substance that modulates the expression of the TSC-22 gene, but also screens for a test substance that modulates the activity of the TSC-22 protein.

In contrast, the screening method of the '440 patent uses a cell that expresses a gene under the control of a myostatin promoter to identify test compounds which inhibit myostatin promoter activity and thereby myostatin expression. *See* the '440 patent, Abstract, and column 3, lines 27-40. Unlike TSC-22 of the claimed invention, there is no separate "target" upon which the test compounds act. Indeed, the only target is the myostatin promoter itself. Thus, the '440 patent does not teach or suggest the use of a cell that (1) has a promoter of a reporter and (2) produces the target protein, in screening methods to identify test substances that modulate the target protein's expression and/or activity. Therefore, even if the '440 patent is combined with the secondary references, Ihara and Flyvbjerg, one of ordinary skill in the art would not have arrived at the claimed screening method.

For at least these reasons, Applicants respectfully submit that the Office has not established a prima facie case of obviousness and request withdrawal of this rejection.

In addition to making the rejection, the Office also addressed Applicants' previous argument that the model of Ihara et al. is not an appropriate model for diabetic nephropathy. In response, the Office contends that:

> regardless of animal models employed, treatments for diabetes would be expected to reduce this complication in humans, i.e. simply treating the disease would reduce any complications of the disease. Accordingly, finding new treatments for diabetes would comprise an obvious way to

> find new treatments for renal disease of which diabetic nephropathy is the major one.

Office Action at page 3. Applicants respectfully disagree and provide the following comments.

The present application shows that mRNA expression of TSC-22 is elevated in the kidneys of various renal disease animal models. *See* as-filed specification at pages 73-79, Examples 1-4. These renal disease models include animal models that have diabetes, such as the Wistar fatty rats having diabetes and spontaneously developing diabetic nephropathy (Example 1), but these renal disease models also include animal models that do not have diabetes, such as the SHC rats, which are spontaneously hypercholesterolemic and spontaneously develop renal disease (Examples 3 and 4).

Moreover, Example 2 uses the Zucker fatty rats, which have hyperinsulinemia and spontaneously develop renal disease, but have normal blood glucose levels. *See* Bray, *The Zuker-fatty rat: a review. Fed Pro.* 1977, 36(2):148-153 (Abstract provided). In this non-diabetic renal disease model, candesartan cilexetil, a hypertension drug that is an angiotensin-converting enzyme (ACE) inhibitor, reduces mRNA expression of TSC-22. *See* as-filed specification at pages 75-76, Table 4. That reduction correlates with suppression of urinary albumin excretion, a hallmark symptom of renal damages. Therefore, the present application demonstrates that TSC-22 is implicated in renal disease, regardless of diabetes or insulin status. The present specification further exemplifies a number of renal diseases that are not related to diabetes, such as chronic glomerulonephritis, IgA nephropathy, and so on. *See* as-filed specification, the paragraph bridging pages 30 and 31.

Furthermore, the claimed method selects the test substance that changes the expression level of the insulin gene or the gene under the control of the insulin promoter as a candidate for the prophylactic or therapeutic substance for a renal disease. As discussed above, the insulin gene, or the gene under the control of the insulin promoter, is employed as a reporter for changes in the TSC-22 expression and/or activity in the claimed method. Moreover, as noted above, TSC-22 is implicated in renal disease regardless of diabetes or insulin status. Thus, a compound that modulates TSC-22 expression and/or activity, as a candidate for the prophylactic or therapeutic substance for a renal disease, does not necessarily have an effect on diabetes. As diabetes is not the disease targeted by the claimed screening method, the Office's contention that finding new treatments for diabetes would comprise an obvious way to find new treatments for renal disease appears to be misplaced.

For at least the foregoing reasons, Applicants respectfully submit that the Office has not established a prima facie case of obviousness and request withdrawal of this rejection.

V. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the Office's reconsideration of the application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: February 12, 2010

By: _____

Bing Hai
Reg. No. 57,170
(650) 849-6774

Display Settings: Abstract

Fed Proc. 1977 Feb;36(2):148-53.

The Zucker-fatty rat: a review.

Bray GA.

The Zucker (fatty) rat is one of a group of animals that inherit obesity as an autosomal Mendelian recessive trait. These rats are obese, hyperphagic, and hyperinsulinemic, but blood glucose remains at normal levels. Although these rats eat more than normal rats, their response to the addition of adulterants to the food or after exposure to the cold is more like that of normal rats than rats with hypothalamic obesity. The hypertriglyceridemia which characterized these animals is due to the increased hepatic production of a very low density lipoproteins. Adipocytes are increased in size and in number with the subcutaneous fat depot showing the largest increase in the number of fat cells. Lipogenesis from glucose is brisk in the young animals but declines with age. Enzymatic patterns of glycolysis and gluconeogenesis appear to reflect the altered internal milieu rather than specific defects. Endocrine changes in the fatty rat include hyperinsulinemia, reduced levels of glucagon, hypothyroidis, and impaired reproductive function. A model is presented in which the features of the genetically obese (Zucker) fatty rat are compared with those of animals with hypothalamic obesity.

PMID: 320051 [PubMed - indexed for MEDLINE]